PREFACE

Most presently used anticancer drugs were developed based on their antiproliferative rather than antioncogenic properties and consequently suffer from two major limitations. Many are cytotoxic and cause major thwarted effects owing to their ability to inhibit indiscriminately the growth of fast dividing cells. Drug resistance, the second major limitation of these drugs, arises primarily from the lack of activity against the more slowly growing solid tumors.

The recent explosion of knowledge gained from genes capable of causing cancer, and the pivotal role they play in growth factor signal transduction, have opened up new avenues for rationally designing novel anticancer drugs. One of the best studied signal transduction pathways, which contains a gold mine of anticancer drug discovery targets, is that of receptor tyrosine kinase signaling. A key molecular switch within this pathway is a small GTPase called Ras. Ras mediated the transfer of biological information from extracellular signals to the nucleus and is a major regulator of cell division. Oncogenic mutations in the ras gene are found in about 30% of all human cancers and result in a constitutively activated protein that sends uninterrupted signals to the nucleus. Over the last two decades several approaches have failed to reverse the constitutive activation of the Ras protein. Recently, however, the realization that farnesylation, a lipid posttranslational modification, of Ras is required for its cancer-causing activity, prompted an intense search for farnesyltransferase inhibitors as novel anticancer agents.

Farnesyltransferase Inhibitors in Cancer Therapy describes the efforts of several groups to design, synthesize, and evaluate the biological activities of farnesyltransferase inhibitors. Rational design of small organic molecules that mimic the carboxyl terminal tetrapeptide farnesylation site of Ras resulted in pharmacological agents capable of inhibiting Ras processing and selectively antagonizing oncogenic signaling and suppressing human tumor growth in mouse models without side effects. These agents are presently undergoing advanced preclinical studies. Several important issues, such as the mechanism of action of farnesyltransferase inhibitors and the potential mechanisms of resistance to inhibition of K-Ras farnesylation, are also discussed. Furthermore, the recent observation that K-Ras 4B, the most frequently mutated form of Ras in human tumors, can be geranylgeranylated and that, in addition to Ras, there are other geranylgeranylated small G-proteins that play an important role in smooth muscle proliferation and apoptosis, stimulated the search for inhibitors of a closely related enzyme, geranylgeranyltransferase I. Thus, the current volume also discusses geranylgeranyltransferase I inhibitors as modulators of cell cycle and apoptosis, and as potential therapeutic agents for cardiovascular disease.

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